EFFECT OF PYRROXAN AND BUTYROXAN ON NORADRENALIN STORAGE AND RELEASE IN THE ALBINO RAT BRAIN

M. P. Podosinovikova,
A. V. Lychakov, S. S. Krylov,
and N. T. Starykh

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Pyrroxan [6] and butyroxan [7] are Soviet drugs with marked peripheral and central adrenoblocking properties. The use of these drugs for the treatment and prevention of disease accompanied by an excessive increase in sympathetic tone and, in particular, for the termination, prevention, and treatment of diencephalic and hypertensive crises of sympathicotonic character [3, 5, 9], in allergic dermatoses [1, 2], and in the treatment of the withdrawal syndrome [8, 10] has proved highly effective. From the biochemical point of view the effect of pyrroxan on dopamine and serotonin metabolism in the brain has been studied [14].

The object of the present investigation was to study the effect of pyrroxan and butyroxan on noradrenalin (NA) storage and release in the albino rat brain.

EXPERIMENTAL METHOD

Pyrroxan, in a dose of 30 mg/kg, or butyroxan, in a dose of 15 mg/kg, was injected intraperitoneally into rats. Control animals were given an injection of physiological saline. The rats were decapitated 30 min later and NA determined in brain homogenates. The mediator was isolated from brain homogenates by adsorption chromatography [12]. The NA concentration was determined spectrophotometrically [11]. The brain NA was fractionated into free and bound fractions [13]. The NA concentration also was determined in brain synaptosomes, isolated by the method of Whittaker and Sheridan [15]. Brains from eight animals were used in the experiments. All sucrose solutions contained the monoamine oxidase inhibitor nialamide (10^{-4} M). The isolated synaptosomes were diluted 1:10 with 0.32 M sucrose and centrifuged for 15 min at 20,000g. The residue was resuspended in Krebs—Ringer solution (10 ml) containing 0.18 M glucose to create isotonicity. Exogenous NA was added to the sample in a dose of 20 μg, and the sample was then divided into experimental and control portions. A solution of pyrroxan (100 μg/ml) or butyroxan (50 μg/ml) was added to the experimental sample. The samples were incubated for 15 min at 37°C and centrifuged for 15 min at 20,000g. NA was determined in the residue and supernatant.

EXPERIMENTAL RESULTS

A decrease in the NA level in the rat brain homogenate by 21% compared with the control was observed 30 min after the injection of pyrroxan. Butyroxan caused no change in the Na level in the rat brain homogenates (Table 1).

TABLE 1. Effect of Pyrroxan and Butyroxan on NA Level (in μg/g tissue) in Rat Brain (M ± m)

Drug	Control	Experiment	P	No. of exp. (control/exp.)
Pyrroxan	0,43±0,005	0,34±0,001	<0,05	12/12
Butyroxan	0,42±0,01	0,43±0,005	>0,05	8/8

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TABLE 2. Effect of Pyrroxan and Butyroxan on Levels of Free and Bound NA (μg/g tissue) in Rat Brain (M ± m)

Preparation	Bound NA	Free NA	No. of exp. (control/exp)
Physiological saline (control)	0,199±0,003	0,097±0,006	7/6
Pyrroxan (experiment)	0,173±0,005*	0,071±0,02*	
Physiological saline (control)	0,282±0,03	0,133±0,02	4/4
Butyroxan(experiment)	0,315±0,02	0,177±0,01	

*Here and in Table 3, $P < 0.05$.

TABLE 3. Distribution of NA between Synaptosomes and Incubation Medium (in μg per sample) in the Presence of Pyrroxan and Butyroxan (M ± m)

Preparation	NA in synaptosomes (C_2)	NA in incubation medium (C_1)	$K = \frac{C_1}{C_2}$	No. of exp. (control/exp)
Physiological saline (control)	1,42 ± 0,033	13,52 ± 0,22	9,55 ± 0,25	5/5
Pyrroxan (experiment)	1,07 ± 0,083*	13,58 ± 0,31	16,7 ± 0,94*	
Physiological saline (control)	0,9 ± 0,02	17,1 ± 0,35	19,2 ± 1,2	5/5
Butyroxan (experiment)	0,88 ± 0,03	17,1 ± 0,6	19,5 ± 1,28	

Considering that NA is physiologically active only in the free form [4], the levels of free and bound NA were determined during the action of pyrroxan and butyroxan (Table 2).

As Table 2 shows, pyrroxan lowers the levels of free and bound NA in the rat brain, but butyroxan caused no statistically significant changes in these parameters.

Considering that reuptake plays an important role in the inactivation of NA liberated into the synaptic space, the effect of pyrroxan and butyroxan on the NA content in synaptosomes was studied.

It was found that after incubation of synaptosomes for 15 min in a solution of pyrroxan (100 μg/ul) the NA concentration in the synaptosomal fraction decreased whereas in the incubation medium it was practically the same as in the control. The coefficient K, the ratio of the NA concentration in the medium (C_1) to its concentration in the synaptosomes (C_2), was significantly higher in the experimental than in the control samples. Butyroxan, in a concentration of 50 μg/ml, caused no statistically significant changes in the NA distribution between the synaptosomes and incubation medium (Table 3). Pyrroxan, in the doses used, thus lowered the concentration of the bound form of NA in experiments both *in vivo* and *in vitro*, whereas butyroxan, in the doses used, caused a small increase in the bound NA level *in vivo* but did not affect the distribution of NA between the synaptosomes and incubation medium *in vitro*.

The difference between the actions of pyrroxan and butyroxan on NA storage and release in the rat brain thus revealed makes a useful contribution to our understanding of the essential differences in the therapeutic value of these drugs, noted during their clinical use [3, 9]. This is particularly important because, with respect to their pharmacological characteristics, there is only a very small quantitative difference in the strength of the α-adrenoblocking action of pyrroxan [6] and butyroxan [7], and on those grounds it is impossible to explain the difference in their therapeutic effects.

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EFFECT OF SODIUM HYDROXYBUTYRATE ON BLOOD SUPPLY AND ACTIVITY OF THE INTACT AND ISCHEMIZED MYOCARDIUM

G. G. Chichkanov, A. K. Bogolepov, I. B. Tsorin, and D. D. Matsievskii

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Because of the experimental and clinical evidence that sodium hydroxybutyrate has a marked antihypoxic action [1, 6, 8, 11, 12] it could be expected that it would also have an antianginal effect. Clinical trials have shown, for example, that the compound abolishes painful episodes in patients with acute myocardial infarction and with severe attacks of angina [7, 10]. However, until recently the problem of the effect of sodium hydroxybutyrate (SHB) on the blood supply and activity of the heart had received little study. The investigation described below was carried out in an attempt to fill this gap.

EXPERIMENTAL METHOD

To judge the effect of SHB on the blood supply of the intact myocardium two series of experiments were carried out on cats weighing 2-3 kg, anesthetized with pentobarbital (30 mg/kg, intravenously). SHB was injected intravenously in a dose of 100 mg/kg in the experiments of series I (five animals) and in a dose of 200 mg/kg in the experiments of series II (six animals). The blood supply of the heart was judged from the flow of blood from the coronary sinus [2]. The uptake of oxygen by the heart was determined simultaneously by measuring the arteriovenous oxygen difference photometrically, using a type 036M oxyhemograph.

In the next two series of experiments on cats anesthetized with pentobarbital the effect of SHB on activity of the intact myocardium was studied. An electromagnetic method was used to measure the blood flow in the ascending part of the arch of the aorta by means of a Soviet RKE-1 flowmeter. The following parameters of cardiac activity and the hemodynamics

Laboratory of Pharmacology of the Cardiovascular System, Institute of Pharmacology, Academy of Medical Sciences of the USSR. Bioengineering Laboratory, Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.)
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